BOSTON UNIVERSITY

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Thesis

# PHYSIOLOGY OF THE PANCREAS

Submitted by

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# PHYSIOLOGY OF THE PANCREAS

## OUTLINE

## I- GROSS ANATOMY

The pancreas in man is an elongated gland of reddish-yellow color. The size varies; but the average may be taken as twelve and a half to fifteen centimeters long, from one and one quarter to three and three quarter centimeters thick, and from five to ten centimeters bread. It weighs from sixty to ninety grams.

The pancreas is moulded into shape by adjacent organs which give it a sort of prismatic form. The gland lies in the loop of the duodenum, and is therefore deeply placed in the abdomen, stretching across the posterior wall at the level of the first and second lumbar vertebrae and being almost concealed by the stomach which lies in front of it. It lies almost entirely in the epigastrium,but the tip of its free end or tail comes in contact with the inner surface of the spleen and lies in the left hypochondrium. It is usual to consider the gland as consisting of four component parts, viz., head,neck, body, and tail.

The larger rounded right extremity of the gland forms the head, which accurately fits into and fills the concave side of the sharp curve formed by the second and succeeding parts of the duodenum. The neck is a portion about two and one half centimeters long and curves upward, forward, and to the left from the anterior portion of the

head to unite with the body at almost right angles. The body and tail which together measure about ten to thirteen centimeters cannot really be differentiated from each other, the tail being merely the extremity of the body which turns upward toward the spleen.

The inferior vena cava, left renal vein, and aorta lie behind the head of the gland, while the origin of the superior mesenteric artery, the crura of the diaphragm, the splenic vein, left kidney, and left suprarenal gland are the chief posterior relations of the body. The pancreas is separated in front from the overlying pylorus of the stomach by the lesser omental sac, and the lower portion of the head of the gland is crossed by the transverse colon. (Fig. 1)

The pancreas derives its blood supply from three sources. These are the superior pancreatico-duodenal artery which is a branch of the gastro-duodenal; the inferior pancreatico-duodenal which is a branch of the superior mesenteric; and branches from the splenic artery.

The vagus and splanchnic nerves are the chief nerve supply of the gland. Non-medullated sympathetic fibers from the aortic plexus end around the blood vessels, ducts, and cells.

The pancreas has two ducts, the duct of Wirsung and the duct of Santorini. The main duct or duct of Wirsung

runs deeply embedded in the substance of the gland, somewhat nearer the lower than the upper border, throughout its length from left to right. It is easily distinguished by its white glistening appearance, and the best way to find it is to trace the artery which runs parallel and close to it. It begins by the union of many small ducts from the lobules of the tail, and being joined on all sides by the ducts from the lobules, it increases in size till it reaches its termination at the duodenum. The duct measures about one-quarter of a centimeter in diameter. It follows the course of the gland bending downward and backward, and to the right as it courses through the neck, thence it passes to the posterior part of the head whence it enters with the common bile duct into the second part of the duodenum, about eight to ten centimeters inferior to the pylorus, at the ampulla of Vater.

The duct of Santorini or the accessory pancreatic duct is found in most organs. It is usually much smaller than the main duct and opens into the duodenum about two and one-half centimeters superior to it. In exceptional cases it may be quite large and take over the functions of the main duct. (Fig. 2 & 3)

There have been one hundred and fifty-five cases of accessory pancreases reported to date. Their origin is either from adhesions of the main pancreatic anlage, or from an anamolous anlage. They are in rare cases the site of carcinoma.*

* Moore, R. A., Am. J. of Path., Vol. V, #4, p 407, 1929

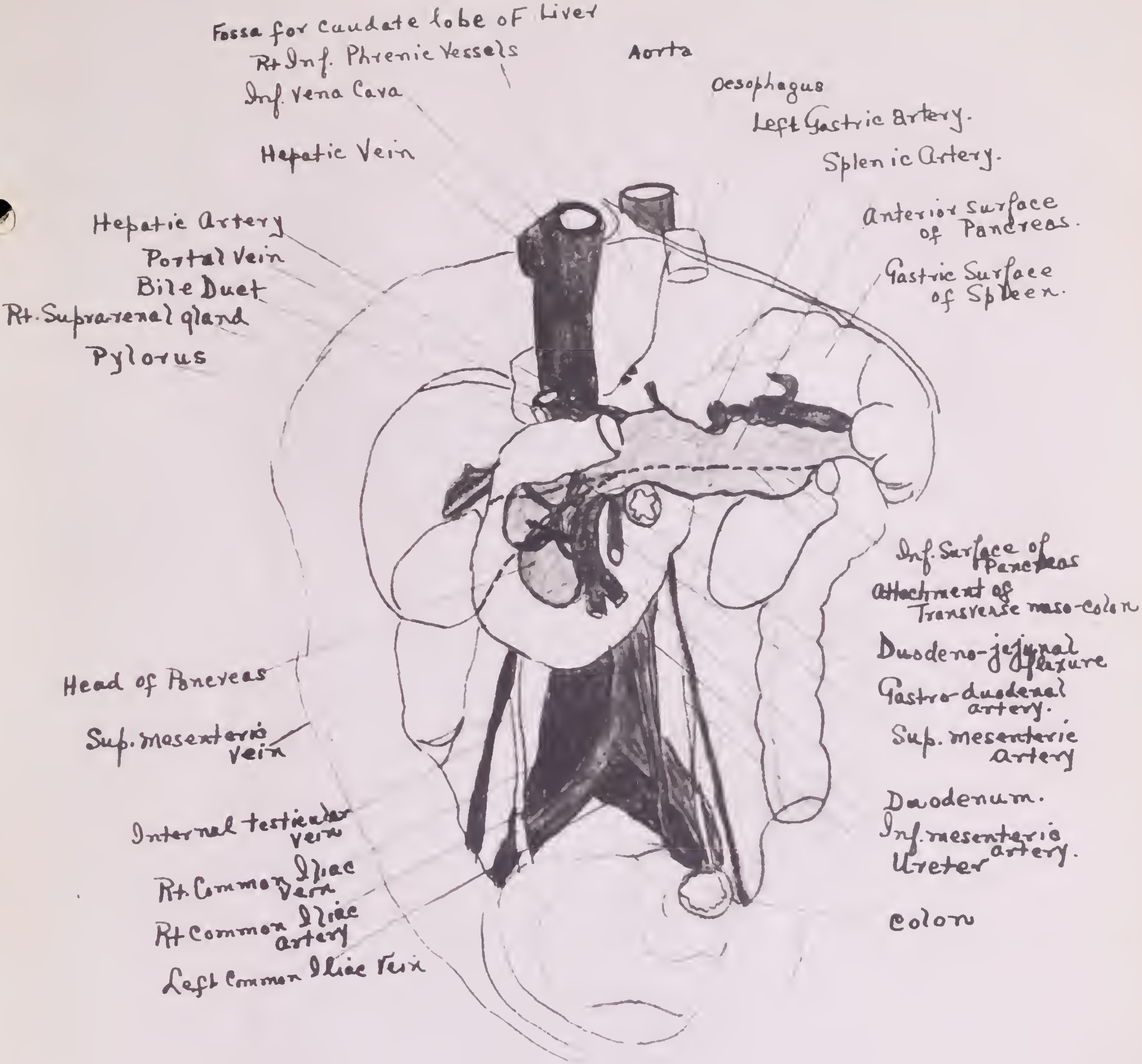

FIG. 1- THE PANCREAS AND ADJACENT ORGANS.(Cunningham p 1195)

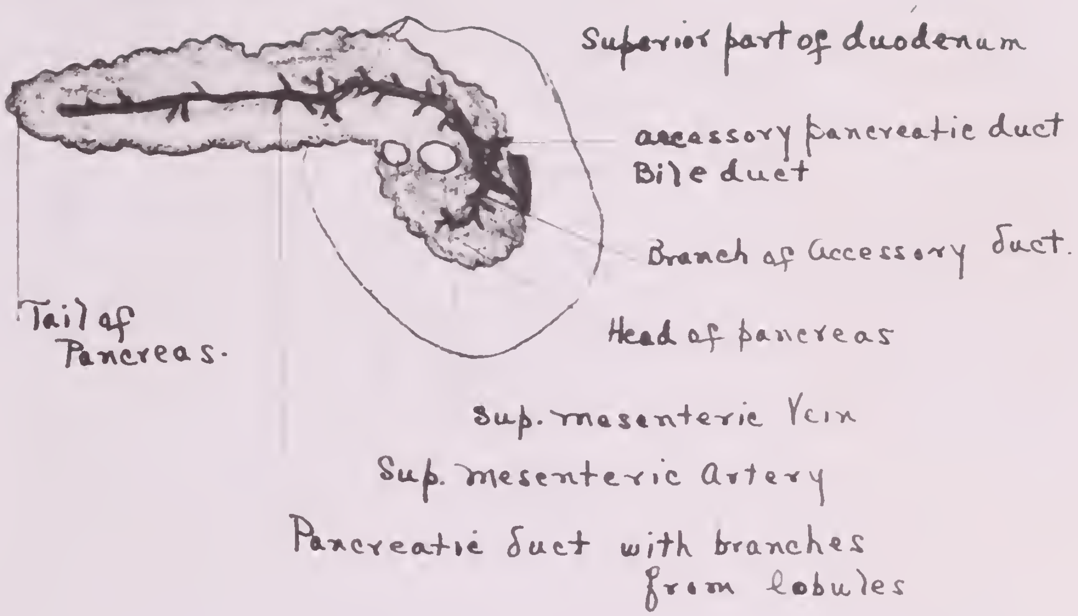

FIG. 2.- POSTERIOR ASPECT OF THE PANCREAS SHOWING DUCTS
( from Cunningham, p 1197 )

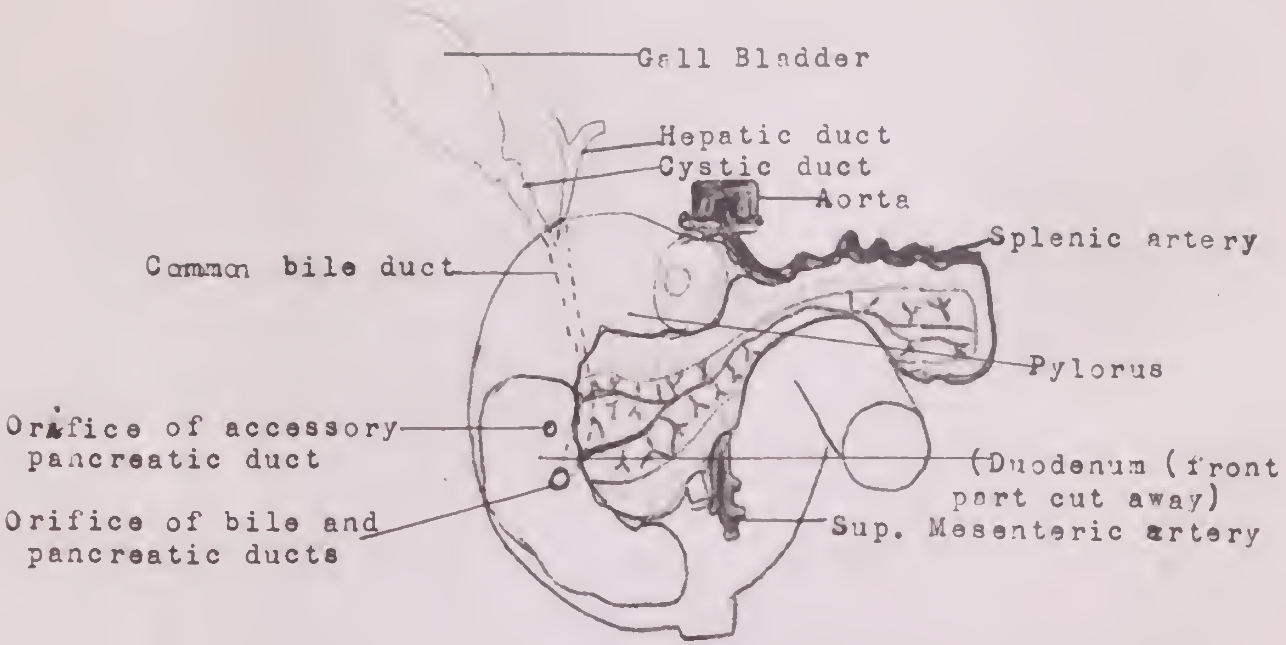

FIG. 3.- RELATION OF ORIFICES OF MAIN & ACCESSORY DUCTS.
(From Kimber, p 272)

## II. EMBRYOLOGY

The pancreas in the adult is a single gland, but it arises in the embryo as two entirely distinct entodermal outgrowths known as the dorsal and ventral pancreases. The dorsal pancreas grows out from the dorsal wall of the intestinal tube at a point a little above the level of the common bile duct. The ventral pancreas grows from the common bile duct at its junction with the intestinal tube and is more or less bilobed. It generally grows to the right of the intestine and there it meets the dorsal pancreas, which approaches it in close relation with the portal vein.

After the dorsal and the ventral pancreases have come together or come in contact with one another, they are related as one. The dorsal pancreas is much larger than the ventral pancreas and grows across the body till it meets the spleen. Thus it gives rise to the body and the tail of the mature organ. It also forms the ventral part of the head which fits into the loop of the duodenum. The duct of the ventral pancreas, by anastomosing with the duct of the dorsal pancreas, becomes the duct of Wirsung. (Fig. 4)

At first the pancreas grows upward behind the stomach and between the two layers of the dorsal mesogastrium, but when the stomach and the duodenum rotate to the right, the

gland becomes horizontal and the opening of the right ventral diverticulum becomes more dorsal. After the rotation of the pancreas to the right, the peritonaeum is absorbed from its dorsal aspect.

The Islands of Langerhans are regarded as portions of glandular epithelium which have been isolated by the invasion and growth around them of mesenchyme. They develop after the pancreatic glands have coalesced and attained a considerable size. They arise as outgrowths from the smaller ducts with which they may retain a solid stalk-like connection.

## III. HISTOLOGY

Microscopic examination shows us that the pancreas is divided into a number of lobules, which are merely held together by their ducts, and by loose areolar tissue.

The lobules, of which this gland is made up, are of the acino-tubular variety. In the centre of each alveolus of the main glandular tissue are spindle shaped cells called centro-alveolar cells. These cells seem to block up the lumina of the alveoli. The alveoli are

composed chiefly of secreting pancreatic cells with coarse zymogen granules near the lumen and striations at the base. The granules are soluble in water and are darkened by osmic acid. The nuclei are round and located at the base of the cell, showing coarse masses of chromatin. The cells rest upon a basement membrane containing basket cells. The centro-alveolar cells are always smaller than the pancreatic cells and contain no zymogen granules. Secretory capillaries extend between the centro-alveolar cells to the pancreatic cells, but do not reach the basement membrane. These capillaries show wide meshes. Nerves, chiefly non-medullated fibers from the aortic plexus, are seen surrounding the blood vessels, ducts, and pancreatic cells. Blood vessels, lymphatic vessels, nerves, interlobular ducts, and lamellar corpuscles are found in the connective tissue which divides the gland into lobes and lobules. (Figs. 5 & 6)

The Islands of Langerhans are round or ovoid areas of paler cells irregularly distributed among the alveoli, and occasionally in the interlobular connective tissue. They consist of coiled anastomosing cords of cells or of irregular masses of pale cells with delicate cell walls and granules finer than those seen in the pancreatic cells. When preserved by special staining methods, two types of cells are distinguished. These are called alpha and beta cells. The alpha cells have oval nuclei with finely

granular chromatin. The beta cells have round nuclei and large chromatin granules. Disturbance of the function of the beta cells and their loss of granulation produces diabetes mellitus, according to work done by Allen, Lane, Bensley, and Schafer.* The Islands are most numerous in the tail of the pancreas, and least numerous in the head region. They are surrounded by an extensive capillary network and produce an internal secretion called Insulin, which is easily received by the blood vessels and plays an important part in carbohydrate metabolism, etc. Ligation of the ducts and degeneration of the alveoli will not cause sugar to appear in the urine, thus showing that the islands are functional and physiologically distinct from the remainder of the organ. (Fig. 5)

The main and accessory pancreatic ducts are lined with simple columnar epithelium, surrounded by a connective tissue layer outside of which is a zone of circular smooth muscle, which helps to form sphincters at the ampulla of Vater. Sometimes goblet cells and small glandular cells resembling mucous glands have been found in the mucosa of the large ducts. The excretory ducts lead from the main ducts to the intercalated ducts between the lobules and are lined with cuboidal epithelium. The interlobular intercalated ducts connect the secretory ducts with the alveoli,

*Evans, Recent Advances in Physiology, pp 291-295

in clusters of which they terminate. They are very slender and their walls are formed of flat cells. (Fig. 6)

In the process of pancreatic secretion, three morphological stages may be recognised. These stages may be definitely separated into the formative, discharging, and storing phases. The cells may also be considered as active and resting, with intermediary stages intervening. The active cells are those either in the process of discharging the formed zymogen, or those which have just discharged it. The resting cells are either advanced in the process of storage, or may be called "secretion-full" and are therefore comparatively loaded with zymogen. If the cells are subjected to injections of secretin continuously, the zymogen granules become discharged from the cells which finally become exhausted.*

Certain histological changes occur in the pancreas during secretion. It has been noted that a normal resting gland is opaque, yellowish-white in color, and of firm consistency. It consists of many alveoli which open into many intercalary tubules and these in turn into wide collecting tubules. The lining epithelium of the intercalary tubules is often continued into the secreting part as the centro-alveolar cells. The secreting cells themselves have a

* Dolley, D., American Jour. of Anatomy, Vol. 35

narrow peripheral zone with the nucleus embedded and strongly basophile; and a central part closely packed with acidophilic granules which are highly refractive. Arousing activity causes signs of fatigue, and the gland then becomes pink, transparent, moist, and soft; the lumen enlarges, the cells shrink and the granules only appear along the border of the cell near the lumen.

Changes have also been noted in the islar tissue. The islands of Langerhans are composed of epithelial cells which stain with difficulty and are supposed to be much concerned with the metabolism of carbohydrates. These are more numerous in actively secreting and exhausted glands, and in the latter case they seem to engulf one alveolus after another of the secreting tissue, thus enlarging themselves. Consequently, the islands of Langerhans seem to represent a stage in the life history of the secreting cells of the pancreas. The cells of the islar tissue contain fine granules which stain somewhat differently than do the cells of the alveolar tissue of the gland.*

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* Starling, Human Physiology, pp 799-802

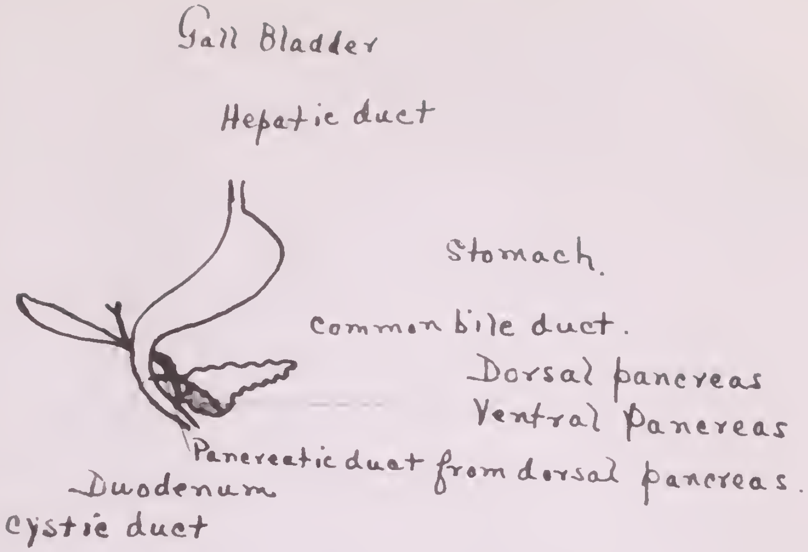

FIG. 4.- PANCREAS FROM A 15mm. HUMAN EMBRYO (Schirmer)

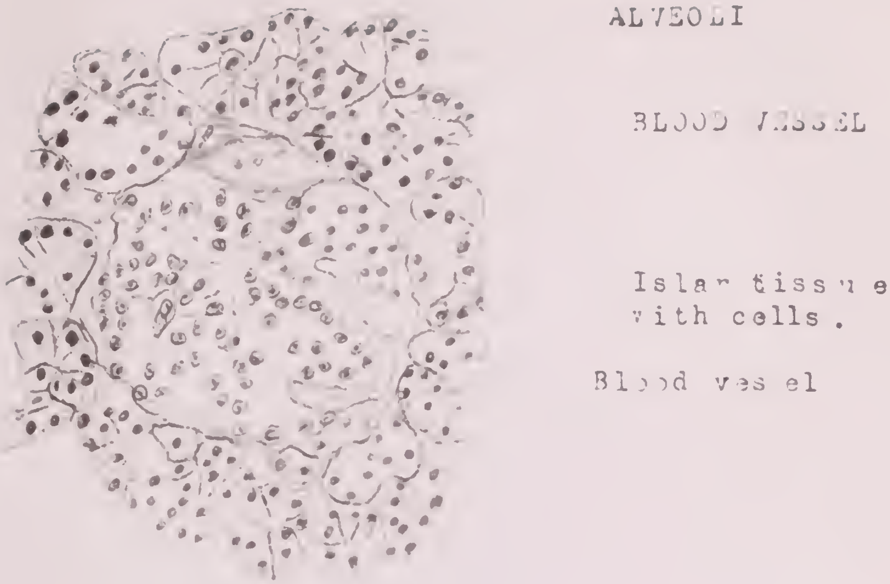

FIG. 5.- ISLAND OF ADULT PANCREAS WITH SURROUNDING ALVEOLI.
(Lewis & Stohr, p 294)

FIG. 6.- SECTIONS FROM A HUMAN PANCREAS.
(Lewis & Stohr, p 292, 293)

## IV. CHEMISTRY OF THE PANCREAS

### 1- Pancreatic Juice

Pancreatic juice is a clear,thin, somewhat viscid fluid. It is alkaline in reaction due to the presence of sodium carbonate. Its specific gravity is 1.005 to 1.010 . About fifteen to twenty-five ounces are secreted in twenty-four hours. It contains few solids, ninety-eight per-cent of which consists of proteins especially serum albumin, serum globulin, and nucleo-protein. A small amount of nucleo-protein is precipitated on acidification. There is also a protein which coagulates at fifty-five degrees C., and another at seventy-five degrees C. It is dependent for its remarkable power on its three principal enzymes, trypsin, steapsin, and amylopsin; each of which has its own specific action and exists in the cell as a pro-enzyme. Its alkalinity varies between 0.1 and 0.14 N. sodium carbonate. It is neutralized by equal quantities of gastric juice, and tends to become poorer in protein and more alkali as secretion proceeds. It has been observed that injections of pilocarpine increase its concentration more than do injections of secretin. (Table I)

### 2- Insulin

Insulin is stable in acid or neutral solutions even at a temperature of one hundred degrees Centigrade. It

is destroyed in alkaline solutions at body temperature, also by trypsin and by pepsin. It gives certain color tests, eg. Millon's Glyoxylic reaction, but these disappear when it is purified. It is carried down by many precipitates, contains sulphur, and an iminazole ring compound as it gives a Pauli color reaction. It has an iso-electric point at pH five. It is precipitated by ammonium sulphate, picric acid, uranium acetate, and other reagents. It is insoluble in most organic solvents and is adsorbed by kaolin and charcoal. It does not dialyze through collodion membranes. It resembles a proteose; and shows the presence of lysine, arginine, histidine, cystine, tryptophane, tyrosine. Its activity is reduced by formaldehyde and nitrous acid, and destroyed by carbon-bisulphide and benzoyl chloride.

## V. THE SECRETION OF PANCREATIC JUICE.

There is practically no secretion in a fasting condition. Flow of the juice starts one to one and one-half minutes after food is taken, increases for two to three hours and then diminishes. The greatest increase is seen when the first portions of digested food escape from the stomach into the duodenum. Weak acids or oil introduced into the duodenum causes a flow of pancreatic juice, the flow being

proportionate to the nearness of the point of introduction into the duodenum. The flow of pancreatic juice proceeds normally till the pylorus relaxes and allows more chyme to enter the duodenum.

The amount of pancreatic juice obtained after a meal varies with the nature of the latter. The difference in flow seems largely determined by the duration of gastric digestion, and therefore by the amount of acid secreted in the stomach and passed on to the duodenum. The pancreas turns out its ferments in constant proportion depending on the amounts of those already present and stored up in the gland. The varied amounts of pancreatic juice after different meals are shown in Table II.

## VI. LOSS OF PANCREATIC JUICE *

Bilious vomiting, intestinal fistulas, or protracted diarrhea may involve the loss of pancreatic secretion, and thus disturb bodily function. The blood before death shows extreme concentration, with a reduced pH or acidosis. This acidosis is less marked where vomiting occurs and is due to the loss of acid gastric juice. Lack of the juice causes ulcers in the duodenal region,and this shows the protective value that the juice has in neutralizing the acid contents discharged from the stomach. Its loss is therefore a menace to well-being.

* Jour. A. M. A. Vol. 94., p 795, 1930

## VII.TABLES I - III

### TABLE I *

### PANCREATIC JUICE RESULTING FROM PILOCARPINE & SECRETIN

| | A | B | | C |
|---|---|---|---|---|
| | | (a) | (b) | |
| Alkalinity: | | | | |
| Number of c.c. of .1N. NaOH equal to 10c.c. of the juice | 12.7 | 12.4 | 9.0 | 5.5 |
| I.e in terms of Na in 100 c.c | 0.2921 | 0.2852 | 0.25 | .1166 |
| Total solids in 100 c.c. ... | 1.6 | 2.25 | 1.5 | 6.4 |
| Total proteins in 100 c.c. .. | 0.5 | --- | --- | 4.8 |
| Ash in 100 c.c. ............ | 1.0 | 1.0 | 1.0 | 1.3 |
| Chlorides in 100 c.c. ....... | 0.285 | --- | --- | 0.2695 |
| Total Nitrogen ............. | ----- | --- | --- | 0.735 |

A. Secretin juice from three dogs. Spec. Gr. 1014
B. Secretin juice collected at beginning (a) and end(b).
C. Pilocarpine juice.

### TABLE II **

### SECRETION OF PANCREATIC JUICE (Walther)

| Hours after meal | 600 c.c. milk | 250 gm. bread | 100 gm.meat |
|---|---|---|---|
| 1 ........... | 8.5 c.c. | 36.5 c.c | 38.75 c.c. |
| 2 ........... | 7.6 | 50.2 | 44.6 |
| 3 ........... | 14.6 | 20.9 | 30.4 |
| 4 ........... | 11.2 | 14.1 | 16.9 |
| 5............ | 3.2 | 16.4 | 0.8 |
| 6 ........... | 1.0 | 12.7 | ---- |
| 7 ........... | ---- | 10.7 | ---- |
| 8 ........... | ---- | 6.9 | ---- |

### TABLE III ***

### COMPOSITION OF PANCREATIC JUICE

| | Glaessner | Wohlgemuth |
|---|---|---|
| Water .................... | 98.72 | 98.70 |
| Solids ................... | 1.27 | 1.30 |
| Coagulable proteins ........ | 0.174 | 0.093 |
| Nitrogen .................. | 0.0983 | 0.0813 |
| Alcohol soluble substances ... | 0.508 | 0.523 |
| (Specific gravity ........... | 1.0075 | 1.0070 |

Ash:- K......1.10% $P_2O_5$ 1.85%
Na ...56.56 $SO_2$ 0.34
Cl....50.75 $CO_2$ 0.11
$SO_3$ .. 2.05

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* Starling, Human Physiology, p 789. ** Ibid.,p 799
*** Bodansky, Physiological Chemistry, p 122

## VIII. SECRETION AND ACTIVATION OF PANCREATIC JUICE

Pancreatic juice makes its appearance in the duodenum about the same time that the first portions of the gastric contents come through the pylorus. The pancreas is subject to nervous and chemical influences, since the activity of the pancreas is not coincident with pleasure and interest of meals as is gastric secretion. The introduction of acid into the duodenum is followed by a flow of pancreatic juice. The introduction of acid in the blood hasn't this effect, however, and therefore it is inferred that acid striking on the mucous membrane of the intestine produces secretin. This passes through the circulation to the pancreas and acts upon its cells, causing a flow of pancreatic juice. Pancreatic juice, as it comes from the gland, may or may not have the power to continue the digestion of proteins. It either has it or acquires it after mixing with the bile and intestinal juice, both these substances being capable of activating the pancreatic juice..

The development of the activity of the juice, as was shown by Pawlow and Chepowalnikoff, is due to a constituent of the succus entericus called enterokinase. This substance acts upon trypsinogin and changes it to trypsin. If pancreatic juice be allowed to stand, it gradually acquires a certain degree of activity. Neutralization hastens its

activity. Lime salts cause activation, the calcium combining with the carbonate present in the juice, further action, however, being unknown. Activation by calcium takes twelve to sixteen hours, so it is not supposed to play any part in the normal processes of digestion. The process of activation is somewhat more complicated than would be supposed from the preceding remarks, and perhaps it would be well at this stage to give further details of the complexity of activation of pancreatic trypsin, eg:

Certain fundic glands formulate an inert body called prosecretin which combines with the hydrochloric acid secreted by the glands and causes the formation of secretin. This latter is absorbed by and passes through the blood stream, goes to the pancreas, and stimulates its cells to secrete and excrete a substance called trypsinogen. This is inert by itself, and is the zymogen of trypsin. In the intestine certain glands secrete a material containing an inert substance which is the parent body of enterokinase. This is inactive but is associated with the alkaline sodium carbonate of the pancreatic juice and there is formed an active substance called enterokinase. This latter acts upon trypsinogen and the interaction of these two bodies results in the production of trypsin.

## IX. FUNCTIONS OF THE PANCREAS

### 1- Digestion

The external secretion of the pancreas possesses digestive properties and is conveyed to the duodenum by one or more ducts. Pancreatic secretion does not seem to be influenced to a great extent by psychic stimuli. The presence of acid chyme in the intestine normally causes active secretion,and Bayliss and Starling in 1902 showed that after nervous communication with the pancreas was destroyed, secretion could be induced by the introduction of acid into the intestine. As this showed chemical control, they prepared an acid extract from the intestinal mucosa, neutralized it, injected it into the circulation of dogs and obtained a copious secretion of pancreatic juice.

The quantity of pancreatic juice secreted varies with the type of food. This is due to an inter-relationship with the gastric secretion. Pancreatic secretion begins when the acid chyme enters the duodenum, the quantity being conditioned somewhat by the amount of acid admitted; the latter in its turn being determined more or less by the character of the food taken. Cessation of pancreatic secretion is followed by a reduction in the digestion of protein and fat.

When carbohydrates are taken into the mouth, ptyalin

acts upon them and converts some of the starch to maltose and malto-dextrin. This requires time and the formation is not complete unless the food is kept into the mouth for half an hour. The reaction of the mouth is slightly alkaline and food passing from here into the stomach meets an acid medium. Here the ptyalin is rendered inactive and there is a tendency for the acid to destroy the outside part of the food masses first, and then gradually eat into the masses. This acid penetration also takes time as cane sugar has to be inverted to glucose and fructose in the stomach. There is no further digestion of starch in the stomach. Fats are hardly at all acted on, while proteins are broken down only as far as the peptone stage.

In the intestine the sodium carbonate of the pancreatic juice neutralizes the hydrochloric acid and then renders it alkaline. Amylopsin of the pancreatic juice breaks down starch to glucose. There is a slight breaking down to maltose by malto-glucase in the mouth, but the intermediate carbohydrates are decomposed, if they are capable of hydrolysis, by the amylolitic enzymes. The galactoses are not acted upon by the pancreatic enzymes but pass to the intestine and influence peristalsis. The juice from the pancreas digests proteins to amino acids, and the fats to fatty acids and glycerine. The secretion of pancreatic juice is in part under the control of the

nervous system through the vagus, but the important control is the action of secretin on the pancreatic cells.

### 2- Oxidation

A second function of the pancreas is to assist in oxidation processes going on in the body. In 1889 certain investigators removed the pancreas from a dog and found that it resulted in the loss of ability to oxidize sugar. Sugar, however, is not oxidized by the pancreatic juice, but needs the influence of the gland itself. A hormone derived from the pancreatic cells enters the circulation and travels to the tissues, and confers on them the power to set free and to utilize the energy latent in the sugar molecules. The pancreas is therefore concerned in bodily co-ordination and energy production in the following way:

Starch is converted to glucose in the intestines, absorbed and carried by the blood stream to the liver where it is converted into glycogen and stored as such. When a muscle contracts it needs fuel, and the glycogen is carried by blood vessels from the liver to the muscles, is converted again into glucose, mixed with oxygen which comes from the lungs, and 'fired' by the internal secretion insulin from the islands of Langerhans. Thus energy is produced. The diabetic has no insulin and so the glucose accumulates in the blood and passes off as sugar dissolved

in the urine. Consequently, when the body cannot oxidize sugar, the constant addition of the pancreatic juice to the blood leads to a condition called hyperglycemia. Then sugar will escape in the urine as the kidneys let it pass when its concentration in the blood exceeds a certain low limit. In fully developed cases of diabetes, all the sugar entering the blood is eliminated unchanged in the urine as glucose, which has not broken down and there follows a faulty fat metabolism and acidosis. When fat is fully oxidized the only end products are carbon dioxide and water. This brings us to the subject of the influence of lowered carbohydrate metabolism.

Utilization of fat is the burning of glycerol and fatty acids. All our natural fatty acids come to us containing some carbohydrates and these burn through beta-oxidation as follows:

$$CH_3.CH_2.CH_2.COOH$$

The beta-hydrogen is replaced by the hydroxyl group. This permits of oxidation and changes the acid to a ketone form and water, eg.:

$$CH_3.CO.CH_2.COOH$$

Then the two terminal carbons split off giving as final products acetic acid, carbon dioxide, and water. In abnormal conditions oxidation ceases when we get to a four carbon group and then the acids are called ketone acid groups, as seen above. The condition back of this is

failure to burn enough carbohydrates, thus causing incomplete fatty combustion. Leading authorities state that this is due either to insufficient carbohydrate to burn as in starvation, or to failure of the body to burn the available carbohydrate as in diabetes. Thus incomplete fatty oxidation causes substances of acid character to accumulate in the blood stream and to produce profound poisoning and acidosis.

### 3- Conversion of Sugar into Glycogen and storage of Sugar.

The process of carbohydrate metabolism is not regulated by ordinary pancreatic extract or external secretion, but it requires the presence of a hormone. This hormone is insulin and has its source in the islands of Langerhans. It causes the blood sugar to fall and prevents sugar from appearing in and being excreted in the urine. It therefore restores the power to oxidize carbohydrate as previously mentioned. The pancreas further aids in the metabolism of carbohydrates by causing storage of sugar in the muscles and liver. It thus plays a great part in the formation of a reservoir for sugar which may be called upon as needed by the tissues or in times of stress. From the above we may note the inter-relationship that exists between the pancreas and other organs concerned with bodily function and well being, the pancreas forming, as it were, a link in an integral chain which regulates our health.

## X. PANCREATIC ENZYMES AND THEIR ACTION

Trypsin is secreted in the form of trypsinogen. This is acted upon by a thermolabile substance called enterokinase and converted into trypsin. Tryptic digestion occurs most readily in a slightly alkaline solution (pH 8.0). Alkaline metaproteins , native proteins, and products of gastric digestion are converted into proteoses, peptones, and amino-acids. Certain peptide linkages, however, are not broken down by trypsin but are acted upon by an intestinal erepsin.

Steapsin is a fat-splitting enzyme secreted partly in the form of steapsinogen. The latter is activated by bile salts, bacteria, saprokinin, and other substances; and through their agency is converted into steapsin. The action of steapsin is facilitated by the highly emulsified state of the fat resulting from the alkali of the intestinal and pancreatic secretions.

Amylopsin is a starch splitting enzyme, active in neutral or slightly alkaline solutions, and converts cooked and uncooked starchy foods through the maltose stage. It is activated by enterokinase.

Lactase * converts lactose into glucose and galactose. This enzyme with maltase plays an active part in the hydrolysis of disaccharides.

Rennin ** is a thin watery fluid, acting in alkaline

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* Physiological Chemistry, Bodansky, 1927, p 123.

** Ibidem.

medium. It takes part in the clotting of milk converting casein into paracasein. It exists in the cells as renninogen and is activated by enterokinase. Van Slyke and Bosworth* found that a molecule of calcium caseinate containing four equivalents of base is split by rennin into two molecules of paracaseinate, each containing two equivalents of base soluble in water if no soluble calcium salt is present. A molecule of calcium caseinate which contains two equivalents of base is split by rennin into two molecules of paracaseinate, each containing one equivalent of base and not soluble in water. They therefore do not regard rennin as a coagulating enzyme, but rather the coagulation is a result of the change in the solubility.

Erepsin is supposed to behave very similarly to trypsin, but its specific action is still a matter for discussion. **

Maltase acts on maltose hydrolyzing it to the glucose stage.***

Invertase acts upon sucrose to some extent and converts it into glucose and fructose. ****

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* Journal of Bio. Chem., Vol. 15, p 231, (1913)

** Bodansky, Physiological Chemistry, p 123 (1927)

*** Ibid.

**** Ibid.

## ACTION ON CARBOHYDRATES:

Pancreatic juice acts on carbohydrates converting them chiefly into hexoses. Some of the carbohydrate is converted into maltose by the action of amylase or diastase. This maltose is acted upon by a second ferment maltase and is thus converted into glucose. Thus it is seen that pancreatic juice can effect the further digestion of the products of salivary digestion. Its chief action is on the disaccharide maltose, but there is some contention as to whether it will act on sucrose or lactose as it contains a very limited amount of invertase or lactase.

If the pancreas is functioning normally, the monosaccharides pass by osmosis or some other means through the intestinal wall, and are there taken up by the portal or the lymphatic circulation to the liver. It may be that some dextrose passes directly to the liver without passing through the intestine. Glycogen is formed almost instantaneously by the liver and may be stored as such; some of it is passed by the blood stream to the muscles and there is broken down to glucose, sarcòlactic acid, etc. Some of the dextrose is reconverted back into glycogen by the muscles.

## ACTION ON PROTEINS:

After trypsinogen is converted into trypsin by the

action of enterokinase, the pancreatic juice acquires a proteolytic activity superior to that of any other digestive juice. The greater part of the protein molecule is broken down to amino acids and the same change is undergone by the albumoses and peptones resulting from the gastric digestion of proteins. A certain amount of resistant or anti-peptone will be found undigested, and this is later acted upon by erepsin of the intestinal juice. After extended digestion by trypsin, polypeptids will be found, and these later break down to form peptids and amino acids. Among the amino acids tyrosine is one of the first to be split off. Trypsin attacks the protein molecule at the -CO-NH- coupling, introducing water at this point and breaking up the polypeptids into simple amino acids. Trypsin will attack only such molecules as are present in the naturally occurring proteins, eg., alanyl glycine, alanyl alanine, alanyl leucine A.

The earlier stages of tryptic activity take place best in an alkaline medium, but later stages best in a neutral medium. This is due to the fact that trypsin in alkaline medium is extremely unstable and so would be destroyed if the reaction were prolonged. Bayliss says that trypsin enters into some form of combination with the protein molecule and so is protected from the destructive action of the alkali. Trypsin carries out its function of hydrolysis at the upper part of the gut, and is destroyed before it reaches the lower part. This is shown by the fact that

the intestinal contents collected at the ilium show little or no proteolytic activity.

In the digestion of proteins it is seen that the mechanism of the pancreas plays a double role, as trypsin acts upon peptones breaking them down to amino acids. Thus it is seen that trypsin continues the work of pepsin--(which breaks proteins down to the peptone stage). Trypsin therefore will continue the digestion of proteins started by pepsin, and will also aid the final digestion of proteins acted upon by by its own influence , bringing about final products as amino acids.

The amino acids may deaminate to urea in the portal system. Urea is non-toxic and is carried to the kidneys and excreted. It forms most of the nitrogenous waste of the urinary tract. The rest of the amono acids is then passed to the blood stream, and thence to the tissues. A change may take place in the hydrogen ion concentration so that the amino acids are attracted to and incorporated into the cells. It is believed that amino acids are stored in the body in some region as yet undetermined since in a protein-free diet the nitrogen output falls. This is soon followed by a secondary fall which is due to the storage of protein being used up, and this in turn is followed by a third fall which is probably the result of the tissue nitrogen being used up.

ACTION ON FATS:

Fats are not acted on by the enzymes that are present in the saliva. The fatty material there, in fact, coats the carbohydrate material and really slows up the process of digestion. The gastric lipase splits a small amount of fat into glycerol and free fatty acids. The material passes through to the duodenum and is neutralized by the alkali of the pancreas and then rendered alkaline by it. Weak alkali here hydrolyzes the fat and the lipase acts much more readily as the medium allows it to obtain its optimum activity. Through the action of steapsin, the fats are broken down into fatty acids and glycerine. This enzyme acts in either alkaline, neutral, or slightly acid medium; but is destroyed by active trypsin. Steapsin is insoluble in distilled water and soluble in glycerine.

Steapsin exists in the gland as steapsinogen and is activated by the bile salts and bile to steapsin. The latter is formed in the presence of sodium carbonate. Bile is a complex excretory product of the liver and the gall bladder. It contains bile acids, pigments, cholesterol, mineral salts, mucin bodies, sugar, etc. Bile acids act in either of two ways: (a) They lower the surface tension and so tend to emulsify fats, that is, break up the molecules held in suspension so that they become widely dispersed and permit of a closer contact being effected. (b) They have a solvent action on soaps and fatty acids in slightly acid medium. The fatty acids react with the sodium carbonate and

sodium soaps are formed. These soaps are capable of absorption and also of lowering the surface tension, thus promoting emulsification of the unchanged neutral fat, eg.:

| | | |
|---|---|---|
| Steapsinogen & Bile acids | produce | Steapsin |
| Steapsin & Fat | " | Fatty acids & glycerol |
| Fatty acids & Na2CO3 | " | Soaps |
| Sodium soaps or bile acids | emulsify | Neutral fats. |

The soaps are soluble in water and so are capable of absorption, and it is probable that most of the fats is absorbed in this form. Intracellular enzymes resynthesize fats as only neutral fats circulate in the blood stream, whence fat goes to the liver by way of the portal vein and is here modified as is shown by the Iodine Numbers taken before and after a meal. In the blood stream, neutral fat is highly emulsified and therefore is hard to detect. Consequently, in diabetes it is difficult to make a smear because of the greasy property the blood has acquired. Although the fat content is then ordinarily increased to 4 or 6%, in severe cases it may reach 27%.

Steapsin of the pancreatic juice will hydrolyze the esters of the fatty acids, such as ethyl butyrate or monobutyrin. Its action on the phosphorized fats or phosphatides is still in question. Pancreatic extracts, however, have been known to split off choline from lecithin, but it is not known if the same property is present in the pancreatic juice itself. It is thought that the action of steapsin, whereby the fats are split, precedes emulsification

by the bile salts as this splitting seems to be a prerequisite to suitable absorption. Work on this,however, is still in the experimental stage, so further comment would be hypothetical. In pancreatic deficiency the fatty acids tend to become unsaturated and we get beta-oxidation. This is further explained under the following topic'ketogenesis'.

## XI. KETOGENESIS.

In diabetes mellitus there are excreted by the kidneys three chemically related substances or "bodies" which may offur in such concentrations in the blood and the tissues as to cause coma, and even death. These bodies are acetone ($CH_3.CO.CH_3.$), beta-hydroxybutyric acid ($CH_3.CHOH.CH_2.COOH$) and beta-oxybutyric acid ($CH_3.CO.CH_2.COOH$) The concentration of these two acids which combine with and diminish the bases in the blood, thus tends to disturb the normal acid-base balance toward the acid side, resulting in acidosis. This condition results when the body has lost to some extent its power to oxidize sugar, or when the sugar necessary for normal metabolism is lacking. Treatment with insulin causes cessation of the production of the ketone bodies and the resumption of the normal power to metabolize sugar. In the absence of sugar, or in the impairment of the power to metabolize it, the ketone bodies are not oxidized to the final products of carbon dioxide and water. Schafer

found by experimentation that the oxidation of sugar assists in the oxidation of the acids mentioned above, and thus sugar is called "ketolytic" or "antiketogenic".

Macallum* finds that, according to Knoop's theory formulated in 1905, the oxidation of a fatty acid in the body proceeds systematically along a chain, attacking first the second carbon atom remote from the COOH of the chain forming a beta-oxy acid, then converting the two proximal links to carbon dioxide and water. Thus with caproic acid:

$CH_3.CH_2.CH_2.CH_2.CH_2.COOH$ plus $O_2$ gives
caproic acid
$CH_3.CH_2.CH_2.CO.CH_2.COOH$ and $H_2O$
beta-oxycaproic acid.

Oxidation of beta-oxycaproic acid gives butyric acid; and this goes through the following steps:

$CH_3.CH_2.CH_2.COOH$ plus $O_2$ gives
Butyric acid
$CH_3.CO.CH_2.COOH$ and $H_2O$
beta-oxybutyric acid.

$CH_3.CO.CH_2.COOH$ plus $4O_2$ gives $4CO_2$ plus $3H_2O$.

When the amount of beta-oxybutyric acid produced is in excess as it is in diabetes, the oxidation of a part of it, at least, is incomplete, and acetone is formed. In each stage of this oxidation the beta-oxy acid is not the immediate and direct product, as there is first formed a beta-hydroxy acid, from which there is formed beta-oxy acid, eg.:

$CH_3.CH_2.CH_2.COOH$ is oxidized first to

$CH_3.CHOH.CH_2.COOH$ and this is further oxidized to

$CH_3.CO.CH_2.CHOH$.

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*Macallum, A. B. The Significance of Ketogenesis, Canadian Medical Assn. Jour. XXII, 3-11, 1930.

The oxidation of fatty acids takes place only in the cytoplasm of living cells, particularly in the liver. It is seen from the above illustration that oxygen is constantly required, and the supply at hand is for the most part used in the oxidation of the sugar and the fat present. As the sugar is much more easily oxidized, a considerable portion of the oxygen available is so used and the rest is left for the oxidation of the fat. If glucose is scanty or wanting, or as in the case of the diabetic, the power to oxidize and store sugar is impaired, almost all the oxygen available is used in the oxidation of fat, and there is formed beta-hydroxy and beta-oxy acids far in excess of the amounts formed when sugar is present. Thus glucose prevents an excessive oxidation of fat.

In the diabetic glucose is not metabolized, and the amount of fat oxidized is greatly in excess of that oxidized in the normal subject. Thus beta-hydroxy and beta-oxy acids are formed in excess, [illegible] escape further oxidation through their free diffusion from the cytoplasmic substrates, and appear in the blood and urine not as free acids but combined with bases. Beta-hydroxy and beta-oxy butyric acids are more soluble in the cytoplasm of the cells in which they are formed than they are in water, and so they readily diffuse from the cells into the lymph and blood to be eventually excreted in the urine. Because of their solubility they are not completely disposed of as carbon

dioxide and water by the beta-oxidation process as are the higher fatty acids including caproic.

It is known that the proportion of beta-hydroxy butyric acid in the blood and urine exceeds the beta-oxy acid. This is explained by the fact that it is the first product of the oxidation, and being very soluble in water and in the cells in which it is formed, some of it cannot be immediately further oxidized and consequently diffuses from them. What remains undergoes further oxidation, yielding beta-oxy butyric acid, a portion of which diffuses out, the remainder being used and completely oxidized to carbon dioxide and water. When the amount of these acids which diffuses out is greater than that normally found in the blood, ketonuria obtains. Since glucose prevents this condition from arising, it is called "antiketogenic". This means that it reduces the amount of ketones to the quantity that the cells are capable of burning before any but negligible traces can diffuse out of them.

## XII. DERANGEMENT OF CARBOHYDRATE METABOLISM -- Diabetes

Minkowski* grafted a piece of pancreas under the skin of a dog's abdomen, removed the pancreas, and noted that diabetes could be prevented.

Hedon** performed similar experiments on animals.

* Arch. f. Exp. Path. und Pharm. Vol. 26, p 399, 1908
** Arch. de Physiologie, vol. 65, p 269, 1894

Forshbach* made an anastomosis of the blood supply of two dogs, removed the pancreas of one of the animals, and found that neither dog developed diabetes. This showed that the pancreas of one dog supplied sufficient hormone to take care of the metabolism of both animals.

Carlson** depancreatized a number of pregnant bitches and observed no signs of glycosuris in any of the animals. The pancreases of the foetuses presumably were active and took adequate care of the metabolism of the mother.

## XIII. INSULIN

### 1- Origin and Source of Insulin

As previously mentioned, the islands of Langerhans contains two types of cells, 'alpha and beta'. The granules of the beta cells are soluble in dilute alcohol, while the granules of the alpha cells are not. In certain fishes eg. Lophius, Myococephalus, Gadus, Hippoglossus, and Pleuronectidae the islands form a separate part of the pancreas and insulin is obtained from this separate tissue only. An insulin-like substance of vegetable origin called 'glucokinin' has already been obtained by Collip*** from yeast and plant tissues. This substance will render an

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* Arch. f. Exp. Path. und Pharm., Vol. 60, p 131, 1909

** Jour, of Bio-Chem., Vol. 17, p 19, 1914

*** Evans, G. Recent Advances in Physiology, p 285

animal hypoglycemic and the blood sugar of this animal, if injected into a second animal, will render the latter also hypoglycemic; and so on in series if repeated.

The main source of insulin at present is the pancreases of cattle. Fetal pancreases also produce active preparations of insulin. Collip's method of obtaining insulin consists in fractional precipitation with alcohol. Doisy, Somogyi, and Schafer modify collip's method by further purifying insulin by precipitation at the iso-electric point, ie., about pH 5.0 **

## 2- Isolation of Insulin

A group of active students in Macleod's laboratory at the University of Toronto isolated insulin in 1922. Work had previously been done in the United States, in an attempt at isolation, by Scott, Clark, Kleiner, Kramer, Merlin and others; but the destructive action of trypsin proved the main obstacle in obtaining active preparation of the pancreatic hormone.

Banting and Best proceeded to offset the effect of trypsin. They ligated the pancreatic ducts in dogs, allowed the acinous tissue to degenerate, performed conplete pancreatectomy after a few weeks, prepared extracts from these pancreases, injected the extracts intravenously or subcutaneously into normal and diabetic animals, and found

** Jour. of Bio. Chem., Vol. 55, Proc. 31, 1923

that it caused a reduction of the blood sugar, and otherwise relieved diabetic symptoms. Collip joined Banting and Best and developed methods for the preparation of extracts suitable for use in human diabetes.

The amount of insulin normally liberated from the islar tissue of the pancreas corresponds to the amount of carbohydrate to be dealt with. The liberation of the insulin is controlled by influences reaching the pancreas by way of the vagus and the splanchnic nerves.

### 3- Standardization of Insulin *

Typical insulin should possess certain properties. It should immediately reduce the blood sugar of fasting rabbits, and when convulsions ensue they should be at once removed by intravenous injections of glucose. When given to depancreatized animals, all symptoms of diabetes should rapidly disappear; and if carbohydrates are given, the respiratory quotient should rise and glycogen should be deposited in the liver. A unit of insulin is now calculated by determining the fall in blood sugar,in a fasting rabbit, in five hours, as compared with the fall induced by a standard preparation, of which one-eighth of a millimeter is known to contain one unit.

* Evans, G., Recent Advances in Physiology, p 297.

### 4- Function of Insulin

Insulin keeps a check on the glycogen that is being transformed into sugar, and enables the tissues to utilize this sugar. It also plays an active part in fat metabolism. When the pancreas is removed, this check is absent and ths system is saturated with sugar but cannot utilize it. The hormone acts directly on the liver and does not act on it through the medulla. Insulin also seems concerned with fat metabolism as many patients with mild diabetes often suffer from lipemia, especially when the carbohydrate intake is reduced. Fat does not overflow into the urine and so cannot readily be detected. It has been shown that there is an increase of fat between the blood stream and the outflow from the tissues, the lipoids all being increased in diabetic lipemia. In the treatment of those cases it takes a considerable time for the blood fat to become normal, which is less than 1%. Insulin, as Fisher has shown, cannot replace the pancreas. Dogs with pancreas removed can be kept alive for some months through the use of insulin, but they gradually lose weight. Insulin, therefore, does not tell the whole story as something else must be mixed with the hormone in the pancreas. If the dogs are fed chopped-up raw pancreas at the time insulin is being administered to them, it is found that they are then kept normal.

## 5- Action of Insulin

Administration by mouth is ineffective, but hypodermic injections of insulin cause a fall in the blood sugar level rapidly for the first thirty minutes. In animals previously starved for twenty-four hours and given large doses, the blood sugar level falls to 0.04% or lower and we have hypoglycemia. In this case the sphincters are relaxed, the animal shows signs of restlessness, violent barking, extreme hunger, convulsions, coma, rapid shallow breathing. After a series of convulsive attacks each lasting one-half to one minute with alternating coma periods, the convulsions become more feeble, the body temperature falls, the animal dies of respiratory failure, and rigor mortis sets in at once. Insulin relieves the symptoms of hyperglycemia, glycosuria, acetonuria, acidosis; produces marked improvement in the utilization of carbohydrates and in the deposition of glycogen in the liver; improves fat metabolism and the conservation of tissue proteins. In man overdoses of insulin give rise to hunger pains, fatigue, faintness, tremor, anxiety, temporary delirium, pallor or flushing, profuse sweating, and in severe cases deep coma. It restores the acid-base balance of the blood and thus is almost a specific for diabetic coma. Here the alkali reserve is low and the patient is therefore subject to severe acidosis and coma. Injections of suitable amounts of insulin will

lower hyperglycemia resulting from adrenaline, piqûre, ether, morphine, asphyxia, glucose injections, and pancreatectomy. In the diabetic patient it restores carbohydrate metabolism to normal and allows the liver to carry a store of glycogen. It causes ketone bodies to disappear from the urine and breath. When the pancreas is functioning adequately, Insulin produces some abnormal effects due to the presence of an excess of the hormone in the body. This will result in lowering both the blood sugar concentration and the glycogen content of the liver and muscles. (Data of Table III) The lowering of liver glycogen is due to the effects of lowered blood sugar in the central nervous system, from which efferent impulses pass to the liver by way of the sympathetic nervous system. Paralysis of these nerves by ergotamine, when followed by insulin , will give a very abnormal fall in blood sugar.

Insulin causes an abnormal fall in the organic phosphorous of the blood. There is also a formation of organic phosphorous esters in the corpuscles; the phosphorous being derived partly from the inorganic phosphate of the blood, and partly from that withdrawn from the tissues. It results in some glucose going to form lactacidogen. In treating diabetes one should combine insulin with glucose in order to obviate the occurrence of coma and convulsions. Some caution is also recommended in its use, as prolonged use predisposes to premature arterio-sclerosis. This is why many clinicians tend to control diabetes by diet, and give only occasional treatments with insulin.

### 6- Dosage of Insulin

A unit is that amount of insulin which will lower the blood sugar of a normal two kilogram rabbit to 0.045 grams in three hours. The rabbit must be fasting for twenty-four hours. The above is the laboratory or the physiological unit, the therapeutical or clinical unit being one-third of that amount.

### 7- Usual method of giving Insulin.

Give subcutaneous injections of one unit daily for each one and one-half to three grams of glucose excreted. This is based on the average output of two or three days. If sugar continues to be excreted, increase the dosage till the urine is sugar free or nearly so.

### 8- Treatment with Insulin

If too much insulin is given it is followed by serious symptoms requiring immediate attention, the ultimate effects being coma and death. Injections of glucose relieves these effects. Indiscriminate use of insulin is dangerous, and proper diet is the better method. If diet fails, combine insulin with restricted diet. In cases of acidosis and coma it is necessary to give insulin immediately. If an operation is necessary, sufficient insulin should be given to keep the urine sugar free till the patient recovers; otherwise there will be grave danger of infection setting in.

## XIV.......OTHER EFFECTS OF INSULIN FUNCTION

Insulin has a vaso-dilator effect on the small capillaries and the more rapid passage of glucose into the muscles is thus due to this action on the muscle capillaries.*

Insulin itself does not seem to have a diuretic effect when injected with pituitrin. The results are influenced greatly by the size of the dose, and by the amountsof water and of carbohydrate consumed. Insulin therefore, affects the diuresis only indirectly**.

Insulin seems beneficial in treating pernicious anemia if given in conjunction with liver or liver extract. It is particularly useful in severe cases of anorexia where there is difficulty in taking liver.***

J. Fromut and G. Mouriquand, Paris, in December 1929, reported good results in treating five cases of Parkinsonian Cachexia with insulin injections, ranging from six to twenty units.****

Insulin injections cause a rise in systolic blood pressure. This rise is believed due to a hyper-suprarenalism resulting from the central irritation probably localized in the medulla or thalamencephalon *****.

Insulin injections lower the leucocyte count. The leucocyte count is high in coma, low in insulin shock ******.

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* Physiol. Abstracts, Vol.13, p 295

** Chemical Abst., Vol. 22, 3458

*** Varga, V., Paris, Med., Vol. 19, p 249, 1929

**** Jour. A. M. A., Vol. 94, p 276, 1930

***** Brems & Holten, Bibliotek for Laeger, Copenhagen, Vol. 121,p 463, 1929

****** Ottow, M. Jour. A. M. A. Vol. 93,p 1773, 1929.

In diabetic children oral administration is effective but works more slowly than do subcutaneous injections. The sugar in the urine disappears before the blood sugar decreases. Latest researches indicate that up to thirty units of insulin in tablet form can be absorbed in twenty-four hours if placed under the tongue. This shows that insulin is not destroyed by the salivary secretion, and indications are that it is active until it gets to the liver and there it is rendered inert or destroyed by the liver cells. *

XV. -------------- TABLE III

GLYCOGEN LOWERING DUE TO INSULIN
(according to Dudley & Marrian**)

| | Glycogen % Normal Rabbit | Insulin Rabbit |
|---|---|---|
| HEART | 5.53% | 1.86% |
| MUSCLE | 0.26 | 0.54 |
| LIVER | 0.57 | 0.00 |

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* Journal A. M. A., Vol. 94, p 370, 1930

** Evans, G., Recent Advances in Physiology, Page 290.

## XVI. METHODS OF PREPARING INSULIN

### 1- Collip's Method

Collip extracts with alcohol, then evaporates the extract in vacuo to a small bulk, and next removes the fat which has separated. He then adds alcohol until eighty per-cent of the original volume is reached and the protein is precipitated. He now adds more alcohol to precipitate the insulin.

### 2- Dudley's and Starling's Method

They extract with alcohol, rendered slightly alkaline with sodium bicarbonate. The filtrate is then acidified with acetic acid and evaporated to a small bulk to remove the fat. Alcohol is now added till eighty per-cent of the original volume is reached and the protein is precipitated. More alcohol is then added and the insulin precipitates when the alcoholic content reaches ninety-two per-cent of the original volume.

### 3- Dudley's Method

Dudley purifies the crude insulin in the above cases by adding picric acid till the insulin is precipitated as insulin picrate. He then adds alcoholic hydrochloric acid and obtains insulin hydrochloride. Acetone is added and the hydrochloride is filtered off. He now washes with acetone, then with ether; and dries.

### 4- Dicken's and Dobb's Method

Mince fresh pancreas with picric acid, and extract with acetone. Then distill off the acetone and solid insulin picrate is left. This is purified by Dudley's method above.

Of the above methods Collip's is probably the best known and most widely used. If one wishes to have insulin that is positively pure, it is advisable to use either the method of Dudley or that of Dickens and Dobb, in this way we get an amorphous powder which is pure and readily soluble in water. As insulin thus prepared has no impurities one can better experiment with it and be sure that any reaction caused by it is due to insulin alone and not to a mixture of insulin and other substances.

## XVII. DIABETES MELLITUS

Diabetes mellitus is a disease of metabolism, especially of carbohydrate metabolism, in which the normal utilization and oxidation of the carbohydrates are impaired, resulting in an increase in the sugar content of the blood and subsequent glycosuris. There is a tendency to subsequent disturbance of the fat metabolism with resulting acidosis. The

intestinal enzymes convert the starches and sugars of the food into monosaccharides which pass to the portal circulation, the major portion of the monosaccharides remaining in the liver where it is converted into glycogen and stored as such . Part of the sugar is stored as glycogen in the muscles.

The appearance of sugar is influenced by the carbohydrate intake and by the nervous system. Regarding the latter, Claude Bernard* showed that the efferent path of this influence was through the splanchnic nerves, and the afferent path through the vagus. Lesions of the nervous system disturb the internal secretion of the pituitary and affect the sugar present. Diabetes mellitus, once established, is influenced by the general condition of the nervous system. Mental worry, strain, anxiety, etc., may have a marked effect. The most important influence on sugar metabolism is the internal secretion of the pancreas. This is opposed by the action of the suprarenals, thyroid, and the posterior lobe of the pituitary. Disturbance of this function of the pancreas is the essential feature in diabetes mellitus. Many other factors influence the appearance of sugar in the blood and urine, eg.: Liver and kidney impairment, obesity, head and leg injury, acute fevers, septic conditions, gout, syphilis, hereditary influences, sex, race; kidney, nerve and liver poisons; asphyxial agents, arsenic, and strong sodium chloride injections. It is therefore

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*Starling, Human Physiology.

advisable to consider these factors whenever a case of diabetes is suspected.

Total excision of the pancreas produces diabetes mellitus. The tissues become extremely prone to infection and healing of wounds without suppuration is almost impossible. Excision causes five to ten per-cent of sugar to appear in the urine. Emaciation follows, and death usually ensues at the end of two or three weeks. The excretion of sugar is due to excess sugar in the blood. This condition will persist even when the animal is starved or fed on a pure protein or on a protein and fat diet, and shows that this excess sugar is due to a breakdown of the proteins ingested or of the tissue proteins. The carbohydrate tolerance becomes abolished and glycogen disappears from the liver, although the liver cells are bathed in blood containing excess sugar which cannot be utilized nor converted into glycogen. There is then incomplete oxidation which results in the accumulation of fatty acids. Morimoti** says that the fat and lipoid content of the blood of animals decreases after total excision of the pancreas, but they are markedly increased after insulin injections. The corpuscular content is not changed, he adds, nor is the ratio of cholesterol to total lipoids changed in either of the above cases, as the change takes place in the plasma.

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** Morimoti, M. Arch. f. d. ges Physiol. 219, p 733, 1928

The external secretion of the pancreas is not concerned with sugar metabolism. This is shown by noting the effect of transplants. A transplant with ligature of the ducts will not cause appearance of sugar in the urine. Houssay, Lewis, and Foglia* state that pancreatic grafts, regardless of the size of the grafts, will reduce the blood sugar level,but not below the normal limits.

The symptoms of diabetes mellitus are: Thirst, voracious appetite, lumbar pain; dry and red tongue, saliva scanty, constipation, emaciation, skin dry and harsh, pulse high, temperature low, pruritis; excess urine with specific gravity 1.030 - 1.035, containing ketone bodies, glycogen, albumin, gas, fat, increased solids and ammonia. There is diminished resistance to infection, and inability to assimilate carbohydrates. The breath may smell of acetone.

The following are some of the chief complications of diabetes. Cutaneous infections, coma, pulmonary infection and abscess, albuminuria, oedema of the feet and hands, ocular complications, neuritis, mental disturbances, and reproductive disturbances. The ocular complications include senile cataract, rapid changes in refraction perhaps due to changes in the osmotic pressure of the blood, and retinitis.

A test diet for diabetes consists of one hundred grams of bread with meat, bacon, eggs, butter, green vegetables, cheese, lettuce, coffee, wine. If the urine is sugar free the case is mild, and bread is added from time

to time until sugar appears in the urine, and the limit for carbohydrate tolerance has thus been reached or determined.

Diagnosis of diabetes is made by means of the following:

1- The D-N Ratio will determine when the power to assimilate carbohydrates is almost entirely abolished. The D-N Ratio means that the nitrogen output parallels the sugar output. As the sugar becomes greater in diabetes, so does the nitrogen output, and this shows that sugar is being manufactured from protein. Howell* gives the D-N Ratio as 3.65 to 1. This ratio is determined from the results obtained from a pure protein and fat diet.

2- The Respiratory Quotient is lowered in diabetes. The production of dextrose from protein needs the use of oxygen, and there will be oxygen taken in which will not appear as carbon dioxide in the expired air. The oxygen has been used up by the protein to form carbohydrate, so that in severe cases the respiratory quotient falls below 0.7.

3- The carbon dioxide tension in the alveolar air is reduced below twenty eight mm. of mercury in severe cases of diabetes. This tension is normally thirty eight to forty-five mm. of mercury.

4- Blood examination aids the diagnosis as fat, lecithin, and cholesterol may appear in increased amounts. A diabetic blood smear will remain unstained, or otherwise stains pale or greenish-yellow when subjected to Bremer's test. (Smear, fix, stain in 1% aqueous solution of Congo Red). The

blood-sugar will vary from 0.130 to 0.4% and in coma it may rise to 1%. When blood sugar increases to about one hundred and seventy milligrams per one hundred c.c., the assimilation limit is passed and glycosuria becomes manifest. Normal blood contains an average of about 0.085% of sugar.

The following treatment is usually resorted to. Reduce overweight and restrict starchy foods. Keep the patient warm and clean, the bowels regular. Avoid worry and insist on careful diet. Give insulin, beginning with one to five units three times a day before meals, increasing one unit daily until the required dosage is found. Opium may be given for extreme irritability, and arsenic may be given if anemia is a complication. Levulose can be taken in diabetes without causing a marked excretion, and in cases of ordinary glycosuria it may replace cane sugar or glucose in the diet. If diacetic acid appears in the urine, it calls for immediate recourse to alkalis, periods of starvation, and the introduction of carbohydrates to tolerance, and withdrawal of fats and diminution of proteins.

Blotner and Murphy* say that the liver contains a blood sugar reducing substance, active when taken orally, non-toxic, and with an effect on the blood sugar concentration similar to that obtained with insulin. It is said that 180 grams of liver will cause the same effect on lowering the blood sugar of certain diabetic patients as will ten to fifteen

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*Blotner & Murphy, Jour. A. M. A., Vol. 92, p 1332, 1929.

grams of insulin. Gregg* says this may be due to insulin present in the liver.

Weinstein* has demonstrated that the inhalation of pure concentration oxygen decreases the specific gravity of urine and its sugar content, and if given over long periods of time, sugar will disappear completely from the urine. Blood sugar also decreases, diuresis becomes less marked, Pruritis, thirst, and feelings of dryness also disappear after treatment by oxygen inhalation two to four times a day for ten minutes, over a period of three weeks.

In treating diabetes, the physician should provide a suitable, nourishing, and satisfying diet. He should train the patient to maintain a balance between the dosage of insulin and the diet, increasing or decreasing the dosage when necessary. He should test the urine for sugar every morning and evening. He must check the Benedict's solution frequently with corn-syrup and discard it if there is no color change on heating. If diabetes complicates other diseases, he should use insulin sufficient to check the glycosuria; and if acidosis develops it should be used moderately and frequently testing the urine or blood before each injection. Insulin treatment is desirable in cases of diabetes in children. The physician should insist on constant supervision of the patient.

The patient himself will do well to remember the following suggestions. He should consult a physician at

* Gregg, Am. Jour. of Physiol., Vol. 90, p 458, 1929

once. Become acquainted with the principles and details of treatment and learn to examine and test urine. Learn the composition of food stuffs, and weigh the food taken. The patient should learn the technique of hypodermic injection and give them himself. A number thirty-six gauge needle is most desirable. Sterilize the syringe and needle before every injection and wipe the skin with alcohol before injecting the insulin. He should use complex forms of starch,such as green vegetables. These are not rapidly converted into glucose and thus will not overtax the liver rapidly. The treatment must be continued as long as it is necessary.

## XVIII. METABOLISM IN DIABETES

There is failure of normal oxidation and combustion of the carbohydrates. The sugar seems to have a diuretic action resulting in the patient drinking much water in an attempt to carry off the sugar. Thus we observe the appearance of polyuria, which in its turn causes excessive thirst. The excess sugar renders the body very susceptible to infection. There is a loss of four and one-tenth calories of energy with every gram of sugar excreted in the urine, and for this reason the patient is really underfed.

Failure in the combustion of carbohydrates is shown by the respiratory quotient of the patient. This indicates that the patient has lost the power of storing glycogen, to some extent, and thus the energy required must be supplied from protein and fat. The combustion of the proteins means a severe task on the system, and, as a result of incomplete combustion, there follows an accumulation of toxic products and their poisonous effects. Beta-oxybutyric acid which is the source of diacetic acid and acetone is one of the chief products formed. Acidosis is supposed to be the result of the enolic group in diacetic acid, and is said to react upon the respiratory centre causing deranged metabolism.

Metabolism in diabetes seems to be benefited by the action of alcohol. T. C. Hunt* says that absorption of brandy lowers the fasting blood sugar in the diabetic. It stimulates the gastric secretion and increases the production of secretin and pancreatic secretion. Thus it provokes an output of insulin. Alcohol, he says, is of value in diabetic coma and can be substituted for or added to a part of the diabetic diet without detrimental influence on the hyperglycemia.

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* Hunt, T. C., The Lancet, London, Vol. 1, p 121, 1930

## XIX. BLOOD SUGAR

The amount of sugar in the blood is controlled and regulated chiefly by the internal secretion of the pancreas. The blood sugar level is normally from eighty to one hundred milligrams per one hundred cubic centimeters of blood. Glucose passes through the intestinal wall and gets to the blood stream by way of the portal system, thus causing a rise in blood sugar as noted by tests taken before and after meals. This rise would persist were it not for certain mechanisms, eg: (a) Oxidation processes which maintain a normal blood sugar level and breaks down glucose to carbon dioxide and water. This requires the presence of insulin from the pancreatic islands. The carbon dioxide and water are eliminated by the skin, lungs, and kidneys. (b) The excess carbohydrate coming in is changed to storage material, eg. fat, and so it is withdrawn from the blood stream. (c) Carbohydrate is built up from glycogen, the reserve carbohydrate of the animal body. Because of the storage above, there is a withdrawal of the carbohydrates from the tissues and its reconversion to glucose, eg.:

| Intestine------ | Blood stream------- | Cells |
|---|---|---|
| Starch | glucose | glucose---glycogen. |
| Glucose | 100-180 mgm. | (Concentration raised.) |

The storage mechanism in which the pancreas plays such an

important part may be explained as follows:

When the concentration of glucose in the blood increases above that of glucose in the tissues, it passes from the blood stream to the cells. As we increase the glucose, the concentration rises and we force the reaction to go from left to right, thereby increasing and building up the glucose and glycogen in the cell till an equilibrium is reached and

$$C_b \text{ is equal to } C_c$$

As this increases we find that $C_b > C_c$

($C_b$ is the concentration of the blood, $C_b$ is that of the cells)

Due to combustion in the cells by oxidative enzymes the glucose is decomposed to carbon dioxide and water. Now as the concentration of glucose sinks and some glycogen breaks down to form glucose, we find that

$C_c < C_{b\ a}$ and more glucose comes from the blood into the cell. If glucose is not restored, there is finally no reserve starch available and the glucose in the blood is drawn upon. Thus the sugar falls below normal till $C_b$ and $C_c$ are at so low a level that there is a tendency for more rapid glycogen decomposition in order to compensate. Overproduction and non-utilization of glucose may cause $C_b$ to be less than $C_c$ and result in a flow of glucose from the saturated cells into the blood stream and consequently cause a rise in blood sugar. The concentration of glucose

in the intestine is always higher than that of the blood or cells, until the sugar in the gut is all used up and absorbed through the wall.

The sugar content of the blood is derived from the following sources or inlets: (a) carbohydrates ingested, (b) glycogen, (c) fat- 10%, (d) protein- 58%.

In testing for blood sugar after ingestion of varying amounts of glucose, it has been found that the blood sugar levels and curves will vary with individuals, and are worthless unless taken in a series with increasing doses at intervals of three minutes for two hours.

The blood sugar levels for different sugars also vary, eg.:

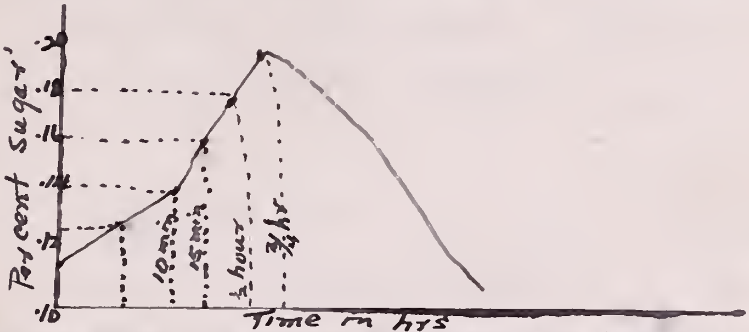
| | |
|---|---|
| Glucose | 150-175 mgm. |
| Galactose | below 40 mgm. for females<br>below 30 mgm. for males. |
| Levulose | 100-125 mgm. (still in experimental stage) |

The galactose level is therefore determined by sex and will vary in a woman as follows:- During pregnancy it decreases to twenty mgm., and during confinement to ten mgm. If the ovaries are removed, it decreases below thirty mgm. at first and then drops to about twenty mgm. In case of endocrine failure it drops first to thirty mgm. then below twenty mgm per one hundred cubic centimeters.

Overproduction of sugar in the blood is prevented by four outlets, the first three of which are chiefly regulated by the pancreas. These outlets are;

(a) glycogen storage, (b) fat storage, (c) oxidation to carbon dioxide and water, (d) renal outlet. (Table IV)

In pancreatic diabetes the blood sugar curve is progressively upwards, and the downward trend is seen only some hours after ingestion of carbohydrates. The following curve will serve as an illustration.



A massive dose of sugar incites the diabetic curve and the test of one hundred grams of carbohydrates, when given, constitutes a supertolerance amount, and is therefore above the assimilation limit.

Pancreatic disturbance is not the only deranged condition which will give rise to blood sugar variations. Adrenal derangement, infection, psychoneuroses, nervous diseases, and faulty metabolism fail to show a blood sugar of over one hundred and twenty mgm. Cardio-vascular diseases tend to increase the blood sugar content. Syphilis with involvement of the central nervous system, and arterio-sclerosis will show a blood sugar of about one hundred and forty-five mgm. Endocrine diseases seem to affect the blood sugar level to a very slight degree, and then only in exceptional cases.

In conclusion it may be said that galactose tolerance is depressed in psychosis, diseases of the nervous system, blood diseases, malignant tumors, liver diseases, syphilis, and all endocrine disorders except hypothyroidism and thyroid disfunction. It is further depressed if any of the above diseases is complicated.. Pituitary failure shows a galactose tolerance increase in sixty four per-cent of cases.

Pregnancy shows its effect on urinary sugar and blood sugar, as eighteen per-cent will show glycosuria, and eighty three per-cent show hyperglycemia. It has been found that sixty-six per-cent of pregnant women show a galactose tolerance of less than twenty milligrams, thirty three per-cent will show a tolerance of less than thirty milligrams, and none will show a tolerance of forty milligrams in one hundred cubic centimeters of blood.

After a sugar tolerance test, according to Depisch & Hasenohrl*, the tension between ths sugar content of the capillaries and the venous blood is lowered in pancreatic disturbances. They also state that a fat diet shows a resistance against insulin and a normal tension.

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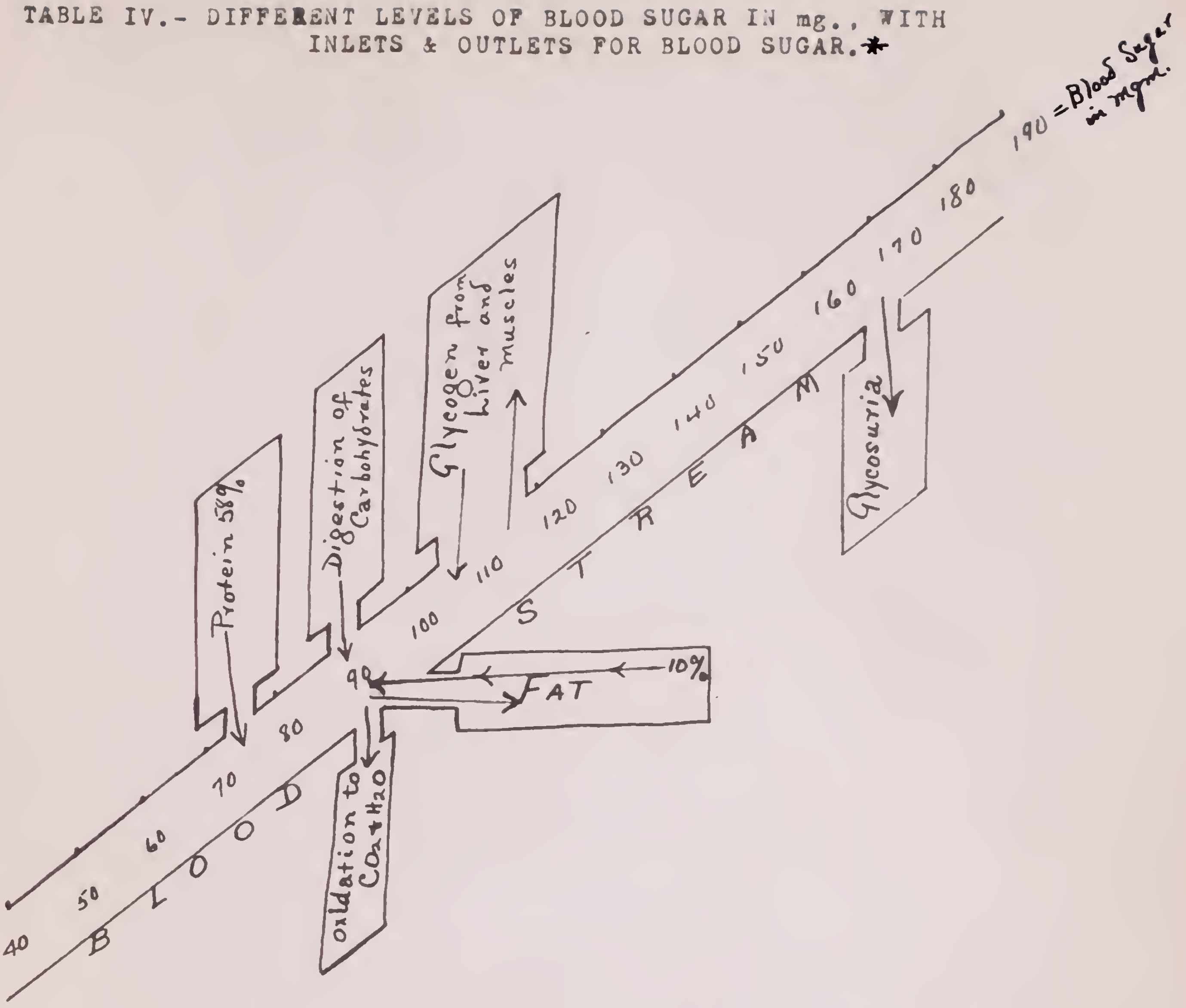
* Depisch, F. & Hasenohrl, Klemsche Wochenschreft, Vol.8, p 1943, 1929. (Berlin)

TABLE IV.- DIFFERENT LEVELS OF BLOOD SUGAR IN mg., WITH INLETS & OUTLETS FOR BLOOD SUGAR.*



Arrows pointing towards blood stream denote Inlets for blood sugar
Arrows " away from " " " Outlets " " "

Inlets and Outlets are approximate.

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*Bodansky, M., Physiological Chemistry, p 210.

## XX. RELATION OF PANCREATIC ISLANDS TO OTHER ENDOCRINE ORGANS.

### 1- Adrenals*

Adrenalin relieves hypoglycemia resulting from excess of insulin. When insulin is given, there is a discharge of adrenalin from the suprarenals;and conversely injection of adrenalin into the circulation leads to the setting free of insulin from the pancreas. This increases the hyperglycemic response and decreases the fall in blood sugar.

### 2- Pituitary

Hypopituitarism is associated with hypoglycemia. Burn, Olmstead, and Logan** have shown that, when pituitary extract is given with insulin, there is a failure of the hypoglycemic reaction which would otherwise be evident. Pituitrin counteracts hypoglycemic convulsions which are caused by excessive insulin injections. Therefore the posterior lobe of the pituitary gland is concerned in carbohydrate metabolism and is thus interrelated with the pancreas.

### 3- Thyroid

Thyroidectomy increases the susceptibility

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* American Jour. of Physiol., Vol. 62, p 162, 1922

** Journal of physiology, Vol. 57, p 318, 1923

to insulin. Burn, Mark, Cramer, and Krause[*] have shown that feeding thyroid extract reduces the glycogen storage of the liver, and makes the liver glycogen more readily available on call. Feeding with thyroid extract also decreases the sensitivity of animals to insulin.

In the discussion of organs of internal secretion, one last point is that over and above the specific effects of the hormones, there appears an inter-relationship between the activities of these glands and reproduction. Further research may prove that there is a chemical integrative system as intricate, delicate, and adaptable as the nervous integrative system.

Turcatti[**] states that it is impossible to produce hyperglycemia if the cortex of the medulla of the suprarenals has been removed. When the medulla is removed, however, hyperglycemia may be produced by pancreatectomy.

[*] Amer. Jour, of Physiol., Vol. 69, p 498, 1924
[**] Revista Medica del Rosario, Rome, Vol. 19,p 269, 1929.

## XXI. SUMMARY

Up to 1922 very little was known of the internal secretion of the pancreas, and the part played by it in health regulation. The external secretion was known to play an important part in digestion. Our modern knowledge of the function of the pancreas has been obtained through careful experimentation on various animals.

I have endeavored to give in condensed form, by way of introduction, the anatomy, histology, and embryology of the pancreas, as well as the histological changes occurring in the active gland.

Pancreatic juice and insulin play a vital part in bodily metabolism, being concerned in digestion of foods, oxidative processes going on in the body, conversion of sugar into glycogen,and the storage of sugar in the liver and muscles.

Both secretions mentioned above are somewhat under nervous control, but the main regulating mechanism is of a chemical nature. The pancreas, as far as is known, is equally important in all groups of animals, as well as human beings. The impairment of the gland will result in the accumulation of toxic products which disturb the normal acid-base balance of the blood. This is followed by acidosis and diabetes, both of which are the result of the body having lost, more or less, its power to utilize and store carbohydrates. Any

serious impairment of the islands of Langerhans results in increased blood and urinary sugar. This is mainly due to incomplete oxidation and faulty metabolism, both of which the normal gland controls.

Insulin was isolated in 1922 by students at the University of Toronto, under the supervision of Doctors Best and Banting. The chief source to-day is from the pancreases of cattle. By subcutaneous or intravenous injections of the hormone, the ill effects of faulty metabolism resulting from impairment of the gland are offset. This is particularly evident in the treatment of diabetes. Insulin may be prepared in different ways, the best known of which is that of Collip. This method is carried out by fractional distillation.

The pancreas seems intimately related to other endocrine organs, and abnormal functions by those organs have an injurious effect on pancreatic function. The adrenals, thyroid, and pituitary glands seem particularly antagonistic in their action. From this it is evident that the pancreas is a sort of link in an intricate integrative system whose function is the regulation of our well being.

The internal secretion of the pancreas largely controls and regulates the amount of sugar in the blood. It, therefore, is the chief factor concerned in carbohydrate tolerance, having a marked action on glucose, fructose, and galactose.

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